

## REMARKS

### Status of the Claims

Claims 4 and 5 have been canceled without prejudice to or disclaimer of the subject matter contained therein. Claim 1 has been amended to recite a method for “culturing” primary liver cells and to include the limitation that a “polycationic polymer” is bound to the CAR material, as previously found in claim 5. Support for this amending language can be found throughout the specification, for example, on page 2, lines 15-17 and in claims 4 and 5 as originally filed. Claims 6-8 and 10 have been amended to correct dependency and antecedent basis. Claim 58 has been amended to recite a method for “culturing” primary liver cells and to include the limitation that “said liver cells attach to said surface.” Support for this amending language can be found throughout the specification, for example, on page 2, lines 15-17 and on page 11, lines 17-19. New claims 62-67 have been added. Support for new claims 62-67 can be found throughout the specification, for example, on page 2, lines 26-27, on page 13, lines 11-13, and on page 15, lines 12-28. No new matter has been added by way of any claim amendments or presentation of new claims.

Claims 1-3, 6-8, 10, 12-16, 58, 61, and 62-67 are subject to examination in the present application, and claims 9, 11, 59, and 60 are withdrawn from consideration as being drawn to non-elected species. Reexamination and reconsideration of the claims are respectfully requested. The Examiner’s comments in the Office Action are addressed below in the order set forth therein.

### The Rejection of the Claims Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-4, 7, 8, and 12-15 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 98/56897 (the ‘897 PCT). Claim 4 has been canceled, rendering this rejection moot as applied to this claim. This rejection is respectfully traversed as applied to claims 1-3, 7, 8, and 12-15.

As discussed above, Applicants have amended independent claim 1 to include the limitation that a “polycationic polymer” is bound to the CAR material, as previously found in

claim 5. As the '897 PCT fails to teach the inclusion of a polycationic polymer in the disclosed surface coating composition for culturing liver cells, Applicants submit that this reference does not anticipate nor render obvious amended claim 1 (and dependent claims 2, 3, 7, 8, and 12-15). Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-3, 7, 8, and 14-16 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,562,616 (the '616 patent). This rejection is respectfully traversed.

As discussed above, Applicants have amended independent claim 1 to include the limitation that a "polycationic polymer" is bound to the CAR material, as previously found in claim 5. As the '616 patent fails to teach the inclusion of a polycationic polymer in the disclosed surface coating composition for culturing liver cells, Applicants submit that this reference does not anticipate nor render obvious amended claim 1 (and dependent claims 2, 3, 7, 8, and 14-16). Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-4, 7, 8, 14, 15, and 61 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,942,436 (the '436 patent). Claim 4 has been canceled, rendering this rejection moot as applied to this claim. This rejection is respectfully traversed as applied to claims 1-3, 7, 8, 14, 15, and 61.

As discussed above, Applicants have amended independent claim 1 to include the limitation that a "polycationic polymer" is bound to the CAR material, as previously found in claim 5. As the '436 patent fails to teach the inclusion of a polycationic polymer in the disclosed surface coating composition for culturing liver cells, Applicants submit that this reference does not anticipate nor render obvious amended claim 1 (and dependent claims 2, 3, 7, 8, 14, 15, and 61). Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

#### The Rejection of the Claims Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-8, 10, 12-16, 58, and 61 were rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over the '897 PCT, the '616 patent and the '436 patent in view of U.S.

Patent No. 6,653,105 (the '105 patent) or published Japanese Patent Application No. JP 04322657 (the '657 application). Claims 4 and 5 have been canceled, rendering this rejection moot as applied to these claims. This rejection is respectfully traversed as applied to claims 1-3, 6-8, 10, 12-16, 58, and 61.

The '105 patent teaches that polybasic amino acids, such as polyornithine and polylysine, and extracellular matrix proteins, such as laminin, collagen and fibronectin, can be used as components of a surface coating composition for enhancing the growth of serum-free C3A cells. The clonally derived C3A cell line "retains most of the characteristics of the human hepatocyte parent C3A line" (column 4, lines 5-7). The '657 application teaches that a cell culture surface "on which many fine protrusions and groves are formed is brought into contact with cells or a tissue(s) selected from connective tissues and nerve, glia, Schwann, skin, muscle, kidney and liver cells" (English abstract). The '657 application further teaches that "one or a mixture of collagen, poly-L-lysine, poly-L-ornithine, laminin, fibronectin, tick plasma, artificial lipid films ... and nerve growth factors" can be adhered to the cell culture surface (English abstract).

Applicants have discovered methods for culturing **primary** liver cells, including providing a polymer composition having a CAR material, and one or more ECM proteins and a polycationic polymer bound to the CAR material, where the CAR material, the one or more ECM proteins, and the polycationic polymer thereby form a cell adhesion promoting surface. In some embodiments, the one or more ECM proteins includes collagen I, and the polycationic polymer includes poly-L-ornithine. As the Examiner has acknowledged, the '897 PCT, the '616 patent and the '436 patent are "lacking particular disclosure about the use of poly-L-ornithine in the surface coating composition in the method for culturing liver cells" (Office Action dated March 17, 2006, page 6, lines 7-8). As discussed above, Applicants have amended independent claim 1 to include the limitation that a "polycationic polymer" is bound to the CAR material, as previously found in claim 5. However, the Examiner contends that it "would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add poly-L-ornithine to the coating polymer compositions of [the '897 PCT, the '616 patent and/or the '436 patent] with a reasonable expectation of success in culturing liver cells because the cell attachment surfaces comprising poly-L-ornithine and collagen type I have been taught and/or

suggested by the prior art of attaching, incubating and growing hepatocytes as adequately demonstrated by the cited references combined” (Office Action, page 6, lines 16-22).

It is well settled in the case law that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. “The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.” *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Applicants respectfully submit that nothing in the ‘897 PCT, the ‘616 patent, the ‘436 patent, the ‘105 patent, or the ‘657 application (or in the knowledge generally available to one of ordinary skill in the art at the time the invention was made), provides the requisite expectation of success required for a *prima facie* showing of obviousness by combining these references.

As discussed above, the ‘105 patent teaches that polybasic amino acids, such as polyornithine and polylysine, and extracellular matrix proteins, such as laminin, collagen and fibronectin, can be used as components of a surface coating composition for enhancing the growth of **serum-free C3A cells**. Serum-free C3A cells (and the human hepatocyte parent C3A line from which the serum-free line is clonally derived) are not primary liver cells, but rather an established human hepatocyte line. As is well known to one of ordinary skill in the art, the requirements for culturing primary liver cells are significantly different from those required for culturing an established hepatocyte line. As also discussed above, the ‘657 application teaches that a cell culture surface having fine protrusions and groves, and coated with one or a mixture of collagen, poly-L-lysine, poly-L-ornithine, laminin, fibronectin, tick plasma, artificial lipid films and nerve growth factors, can be used to culture cells and tissues including connective tissues and nerve, glia, Schwann, skin, muscle, kidney and liver cells.

At best, the teachings of the ‘105 patent concerning culturing of serum-free C3A cells,

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and the disclosure of the '657 application that cells and tissues (including connective tissues and nerve, glia, Schwann, skin, muscle, kidney and liver cells) can be cultured on surfaces having fine protrusions and groves, and coated with one or a mixture of a laundry list of substances, merely invite experimentation. However, an invitation to experiment is not sufficient grounds to reject an invitation as obvious. General statements that poly-L-ornithine, poly-L-lysine, laminin, collagen, fibronectin, tick plasma, artificial lipid films and nerve growth factors may be used in culturing various cell types do not guide the skilled artisan in arriving at Applicants' methods for culturing primary liver cells. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90-91 (Fed. Cir. 1986). Therefore, Applicants submit that a *prima facie* case of obviousness under 35 U.S.C. § 103(a) has not been established, and respectfully request that this rejection be withdrawn.

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### CONCLUSION

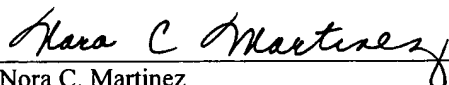
In view of the foregoing amendments and remarks, Applicants respectfully submit that all the rejections have been obviated or overcome and the claims are in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned attorney.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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